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From: Portner, Ginny
Sent: Monday, May 07, 2001 8:26 AM
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-----Original Message-----
From: Portner, Ginny
Sent: Monday, May 07, 2001 8:25 AM
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Double determinant immuno-polymerase chain reaction: a sensitive method for detecting circulating antigens in human sera.
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Double Determinant Immuno-Polymerase Chain Reaction: A Sensitive Method for Detecting Circulating Antigens in Human Sera

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A sensitive method for the detection of antigens in sera, termed double determinant immuno-polymerase chain reaction (double determinant immuno-PCR) was developed, using two monoclonal antibodies (MoAbs), in which the antigens are sandwiched, and a specific DNA molecule is used as a marker. Instead of the antigen itself, the first MoAb to bind the circulating antigens was immobilized. After the biotinylated second MoAb was bound to the antigen, free streptavidin was used to attach a biotinylated DNA to the biotinylated second MoAb. The biotinylated DNA complexed with antigen-antibody-streptavidin was amplified by PCR, and the PCR products were analyzed by Southern blot hybridization after agarose gel electrophoresis. Compared with the conventional enzyme linked immunosorbent assay (ELISA) using soluble intercellular adhesion molecule-1 (sICAM-1) in the supernatant of cultured Panc-1 cells as an antigen, our double determinant immuno-PCR was 10^3 times more sensitive in terms of the detection limit. Not only in culture medium, but also in sera from gastric cancer patients of high sICAM-1 titer, an approximately 10^3-fold enhancement in detection sensitivity was obtained compared with ELISA. In addition, this system can detect the antigen in sera at a level below the detection limit of traditional ELISA methods with high sensitivity. Thus, double determinant immuno-PCR has the significant advantage that it can be readily applied to any antigen-antibody system for which two MoAbs are available.

Key words: ELISA — PCR — Immuno-PCR — Double determinant immuno-PCR — sICAM-1

A very sensitive antigen detection system, termed immuno-PCR, has recently been developed by Sano *et al.*[1] They combined the system of polymerase chain reaction (PCR)[2,3] with enzyme linked immunosorbent assay (ELISA) by using a specially designed chimeric protein with bispecific binding affinity for DNA and antibodies as a linker molecule.[4] The exponential amplification of the DNA attached to the immune complex made it possible to dramatically improve the sensitivity (approximately $\times 10^5$) in the system to detect pure bovine serum albumin with a monoclonal antibody (MoAb). Instead of using the recombinant chimeric protein, Ruzicka *et al.*[5] used commercially available avidin to link the biotinylated antibody to the biotinylated DNA to be amplified. They could detect as little as 10 fg/ml of mouse antibody to apolipoprotein E using this system. A similar approach to detecting the recombinant human proto-oncogene ETS-1 immobilized in ultra thin-wall PCR tubes has also been reported,[6] with a huge enhancement ($\times 10^5$) in detection sensitivity compared to that of conventional ELISA. Since these methods are extremely sensitive in detecting immobilized pure antigens with specific antibodies, they may be of practical use in detecting circulating autoantibodies. However, for the purpose of detecting rare circulating antigens such as tumor-associated antigens, it would be impossible to apply these techniques as described, because a double determinant immunoassay is usually required to detect these antigens. We have therefore developed a double determinant immuno-PCR system using MoAbs. In preliminary experiments using a microtiter well, we failed to obtain enhanced detection sensitivity, mainly because of a high background signal on the first MoAb immobilization. In general, the background signal on the first immobilization in ELISA tends to be higher in a microtiter well than in a pin plate. Here we report a double determinant immuno-PCR system using a pin plate to detect soluble intercellular adhesion molecule-1 (sICAM-1). A 10^3-fold higher sensitivity was obtained with immuno-PCR, compared to that of the control ELISA.

MATERIALS AND METHODS

Cell line A pancreatic cancer cell line, Panc-1,[7] was maintained in a humidified atmosphere of 5% CO_2/95% air at 37°C in Dulbecco's modified Eagle's medium (D-MEM) (Gibco, Grand Island, NY) supplemented with 10% fetal calf serum (FCS) (Cansera International Inc., Canada).

Monoclonal antibodies MoAbs CL207 (IgG_1) and HA58 (IgG_1) were prepared by Maio *et al.*[8] and Hirata *et al.*,[9] respectively. MoAb HA58 was biotinylated by mixing 1 mg/ml of the MoAb in phosphate-buffered saline (PBS) with 0.1 mg of N-hydroxy-succinimidobiotin (Sigma, St. Louis, MO) in 0.1 ml of N,N-dimethylformamide (Sigma). After having been incubated for 4 h

at room temperature, the mixture was dialyzed with PBS overnight at 4°C.[10]

Antigens We used serial dilutions of supernatant from cultured Panc-1 cells as the standard antigen. Twenty-four serum samples were collected from gastric carcinoma patients admitted to our university hospital. Aliquots of serum samples were diluted at 1/200 in PBS containing 1% bovine serum albumin (1% BSA-PBS), and were subjected to ELISA and immuno-PCR.

Template DNA As a template DNA, we used a 253-base-pair (bp) fragment corresponding to nucleotides from 4917 to 5169 of leucocyte common antigen related molecule (LAR), which is a member of the membrane associated protein tyrosine phosphatase family.[11] The DNA was biotinylated by a reverse transcription polymerase chain reaction (RT-PCR) using biotinylated primers. Nucleotide sequences of the primers were 5′-TCCTGGCCTTCCTACGACGG-3′ for the sense direction and 5′-CACGTGGCAGCCTCCAGCAG-3′ for the antisense direction.

ELISA The ELISA system for measurement of circulating ICAM-1 was developed in our laboratory.[9] The first MoAb (CL207 5 μg/ml in PBS) was immobilized at 4°C overnight. The plate was blocked with 3% BSA-PBS at 37°C for 2 h, then Panc-1 supernatant or 1/200 diluted serum samples were added and incubation was continued at 4°C overnight. The plate was washed with PBS containing 0.05% Tween 20 (Tween-PBS) for 5 min twice and with PBS for 5 min once, then biotinylated second MoAb (HA58 1 μg/ml in 1% BSA-PBS) was added and incubation was continued at 37°C for 1 h. Avidin-conjugated peroxidase (Vector, Burlingame, CA) diluted 1/1000 in 0.05 *M* PBS with 0.05 *M* NaCl at pH 8.0, was added and incubation was continued at room temperature for 30 min. Then 1 mg/ml *ortho*-phenylenediamine in 0.1 *M* citric acid/0.2 *M* $Na_2HPO_4 \cdot 12H_2O$ with 1 μg/ml H_2O_2 was added and color was allowed to develop for 5 min, at which time the reaction was stopped by adding 2 *N* sulfonic acid. Absorbance (A) was measured at 492 nm (A492) in a micro ELISA autoreader EAR400 (SLT-Lab Instruments, Austria).

Immuno-PCR Procedures up to addition of the biotinylated second antibody were identical to those in ELISA except for the use of 1 mg/ml salmon testis DNA with 3% BSA-PBS as the blocking agent instead of 3% BSA-PBS alone. The plate was washed to remove unbound biotinylated second antibody, then free streptavidin (Sigma) at 1 μg/ml in 1% BSA-PBS was added and incubation was continued at room temperature for 30 min. The plate was washed with Tween-PBS for 5 min four times, and with PBS for 5 min three times, then biotinylated DNA molecules were added at the concentration of 10^5 copy/ml in 1% BSA-PBS and the plate was incubated at room temperature for 30 min. The pins were washed with Tween-PBS for 5 min five times and with distilled water for 5 min four times. They were detached from the plate and put into 50 μl of PCR mixture in a 500 μl Eppendorf tube. Each tube was subjected to PCR using a DNA thermal cycler (Perkin Elmer Cetus, Norwalk, CT). PCR was carried out under the following conditions: 10 m*M* Tris-HCl (pH 8.3), 50 m*M* KCl, 1.5 m*M* $MgCl_2$, 0.8 m*M* deoxyribonucleotide (0.2 m*M* each), 2 μM of each primer, and 1.25 units of AmpliTaq DNA polymerase. The temperature profile used was: initial denaturation (94°C, 2 min), and 35 cycles of denaturation (94°C, 1 min), annealing and extension (60°C, 1 min). Ten μl of the resulting PCR products were run in a 3% (w/v) agarose gel and transferred to nylon membrane, Hybond N^+ (Amersham, Arlington Heights, IL), in 0.4 *N* NaOH/1 *M* NaCl. The blots were hybridized with ^{32}P-labeled LAR cDNA probe.[12]

RESULTS

Effect of the copy number of biotinylated DNA on nonspecific amplification A double determinant ELISA for sICAM-1 using two MoAbs (CL207 and HA58) with different specificities, which was established in our laboratory, was used in this study to examine the availability of double determinant immuno-PCR. Free streptavidin was employed to attach the biotinylated DNA to the biotinylated second MoAb. A major problem we encountered while developing the immuno-PCR was that even the negative control for the first MoAb (1% BSA-PBS) generated some nonspecific amplification. This signal was not affected by the concentrations of MoAbs or streptavidin, or by the incubation time or temperature for binding of MoAbs, blocking agent, streptavidin, and biotinylated DNA. Also, PCR conditions such as number of cycles and annealing temperature and time, and the compositions of blocking agents and washing solutions did not affect the nonspecific signal. However, the copy number of biotinylated DNA had a marked influence on the intensity of false-positive signals. Fig. 1 shows the results of immuno-PCR with 1% BSA-PBS as a negative control for the first MoAb. Serial ten-fold dilutions of the biotinylated DNA were tested and the conditions except for the biotinylated DNA copy number were the same as described in "Materials and Methods." The nonspecific amplification, which was detected as a 253-bp band, started to appear at 10^5–10^6 copy/ml biotinylated DNA. As the copy number was increased, the intensity of the 253-bp band grew stronger until the PCR amplification was saturated at 10^9 copy/ml of biotinylated DNA. Thus, we employed the condition of 10^5 or 10^6 copy/ml biotinylated DNA for further analyses.

Analysis of the nonspecific amplification We then attempted to clarify which agent in our immuno-PCR

was responsible for nonspecific binding with biotinylated DNA. The biotinylated DNA (10^n copy/ml) was added at each step and each resulting complex was subjected to PCR. As a result, no nonspecific amplification was observed until the biotinylated DNA was applied at the step

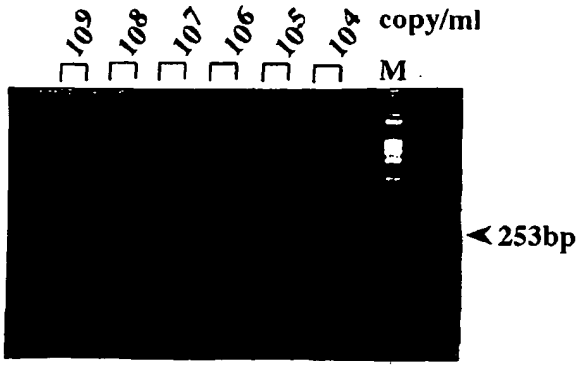

Fig. 1. Effect of biotinylated DNA copy number on nonspecific amplification of double determinant immuno-PCR. A 1% BSA-PBS solution was used as an antigen and conditions except for the biotinylated DNA copy number were the same. Serial ten-fold dilutions of the DNA from 10^9 copy/ml to 10^4 copy/ml were applied to each of two antigen-antibody-streptavidin complexes and amplified by PCR. The PCR products (253 bp) were analyzed by gel electrophoresis and staining with ethidium bromide. M is a DNA molecular weight standard marker (ϕX174-*Hae* III digest).

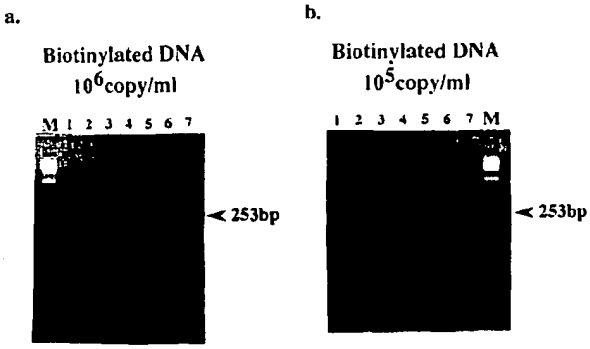

Fig. 2. Step analysis of nonspecific binding. Applied biotinylated DNA copy number; (a) 10^6 copy/ml and (b) 10^5 copy/ml. Lanes 1-6 indicate the steps in which biotinylated DNA was applied. Lane 1, application directly to the pin; lane 2, application after immobilizing the 1st MoAb; lane 3, after adding the blocking agent; lane 4, after incubating with 1% BSA-PBS; lane 5: after incubating with biotinylated 2nd MoAb; lane 6, after incubating with streptavidin (i.e. all steps were completed). Lane 7 represents the application of biotinylated DNA after the streptavidin without the step of incubating with biotinylated second MoAb. M is a DNA molecular weight standard marker (ϕX174-*Hae* III digest).

just after the addition of streptavidin. To determine whether streptavidin alone can cause nonspecific binding, the biotinylated DNA was applied after the addition of streptavidin without the biotinylated second MoAb, generating a nonspecific band with weak intensity (Fig. 2a). The same analysis was performed at 10^5 copy/ml biotinylated DNA. In this case, no nonspecific band could be seen, even after binding of streptavidin (Fig. 2b). These results indicated that streptavidin and the biotinylated second MoAb were mainly responsible for the nonspecific amplification. Thus, we determined that the copy number of biotinylated DNA affording maximum sensitivity without nonspecific amplification is 10^5 copy/ml. The other conditions employed were as described in "Materials and Methods."

Comparison of sensitivity between ELISA and immuno-PCR using Panc-1 supernatant In our conventional double determinant ELISA system of sICAM-1, the reliable cut-off value was 44 ELISA unit/ml (EU). One EU corresponds to 29 pg/ml of purified ICAM-1 (Bender MedSystems, Austria). We prepared serial logarithmic dilutions of the supernatant from Panc-1 cells, with 1% BSA-PBS, from 440 EU to 0.0044 EU to use for ELISA and immuno-PCR. The resulting PCR products were Southern blot-hybridized with a specific probe for LAR cDNA, to detect weakly positive signals. Positive signals were obtained from 440 EU to 0.044 EU, and a negative control for the first MoAb (1% BSA-PBS) did not generate any signal (Fig. 3). This showed that our immuno-PCR could detect ICAM-1 molecules at a level as low as 0.044 EU, and was therefore approximately 10^3 times more sensitive than ELISA.

Comparison of sensitivity between ELISA and immuno-PCR using serum samples For the purpose of the clinical

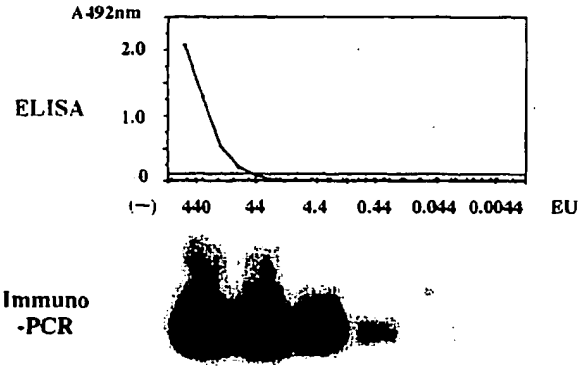

Fig. 3. sICAM-1 detection in Panc-1 supernatant. Serial ten-fold dilutions of Panc-1 supernatant from 440 EU to 0.0044 EU were used as antigens; 1 EU corresponds to 29 pg/ml of purified ICAM-1 antigen. (−) indicates negative control antigen, 1% BSA-PBS.

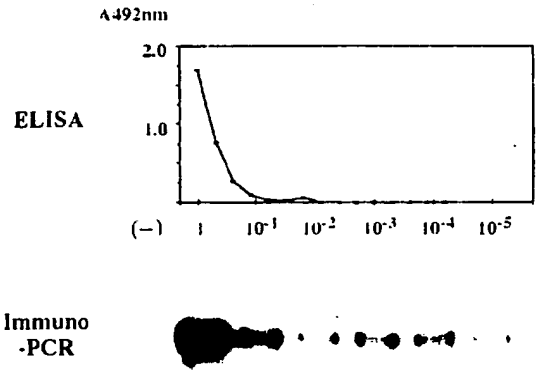

Fig. 4. Comparison of detection limit between ELISA and immuno-PCR using patient's serum as an antigen. Serial ten-fold dilutions of 1/200 diluted serum (which is indicated as 1) were used as antigens. ( ) indicates negative control antigen, 1% BSA-PBS.

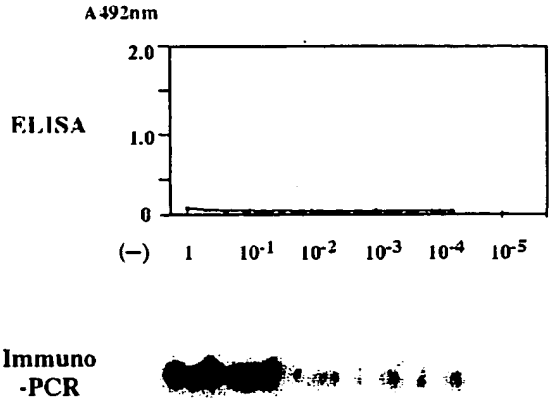

Fig. 5. Detection of sICAM-1 by immuno-PCR in serum below the detection limit in ELISA. Serial ten-fold dilutions of 1/200 diluted serum below the detection limit were used as antigens. ( ) indicates negative control antigen, 1% BSA-PBS.

application of this system, the sera from gastric cancer patients with a high titer of sICAM-1 (over 300 EU in 1/200 diluted sera in conventional ELISA) were then tested. Serial ten-fold dilutions from the 1/200 diluted sera were used for ELISA and immuno-PCR. A representative case is shown in Fig. 4. Whereas the detection limit was at about 1/10 dilution for ELISA, it was at $1/10^5$ dilution for immuno-PCR, with the elimination of nonspecific amplification. Furthermore, as shown in Fig. 5, a patient's serum in which sICAM-1 was below the detection limit for ELISA was also investigated by immuno-PCR. Interestingly, from 1/200 dilution to $1/200 \times 10^4$ dilution clear signals were observed without nonspecific amplification. These results suggest that double determinant immuno-PCR can detect circulating antigens with very high sensitivity, which may enable us to detect rare antigens thus far not encountered.

DISCUSSION

We have developed a new and sensitive system, double determinant immuno-PCR, for the detection of circulating antigens. With the use of the antigen-antibody system of sICAM-1 in sera, approximately 10^7-fold enhancement in detection sensitivity compared with conventional ELISA was obtained in this study. The principal determinant of sensitivity was the copy number of applied biotinylated DNA. Nonspecific binding of the second MoAb and streptavidin was a major limiting factor in applying more biotinylated DNA. The concentrations of the second MoAb and streptavidin had little influence on nonspecific binding at a given copy number of biotinylated DNA (data not shown).

Targets of nonspecific binding of biotinylated second MoAb and streptavidin remain to be determined. The immobilized first MoAb and/or blocking agent could be targets. Some component of serum may interact with the MoAb or streptavidin. The affinity of streptavidin or proteins may vary depending on the physicochemical characteristics of the antibodies and antigens used in the assay system.

In all other techniques of immuno-PCR reported previously,[4,5,9] antigens such as BSA were immobilized directly on microtiter wells[4,8] or ultra-thin-wall PCR tubes.[9] In this study, a pin plate was used to immobilize the first MoAb, and all procedures up to the final amplification by PCR were carried out with the pin. The presence of the pin in the PCR reaction mixture had no effect on amplification (data not shown).

The immuno-PCR methods reported so far, including ours, are semiquantitative and not suitable for strict quantitative analysis. Some quantitative PCR methodologies have recently been developed,[13-15] and applying those methods to immuno-PCR may be useful to increase the quantitative reliability.

In this study, we used sICAM-1 as a model antigen system to examine the sensitivity of double determinant immuno-PCR. However, sICAM-1 may not be the best target if this system is to be applied to diagnostics, because the expression level of sICAM-1 in sera from patients with various diseases is high enough to be detected by the conventional ELISA system,[9,16] and sICAM-1 is expressed not only in the sera of patients with malignant diseases, but also in the sera of patients

with benign inflammatory diseases.[17, 18] A better target for our method might be certain tumor-related antigens for which detection by conventional ELISA has a high specificity but a low sensitivity. For example, circulating antigens which are barely detectable using conventional methods, such as the ErbB-2 product,[19, 20] would be good candidates as target molecules of our method. Our present data indicate that the double determinant immuno-PCR system is highly sensitive and might be useful as a clinical diagnostic tool for early stage malignancy, or to monitor tumor burden in the circulation of patients before and after surgical resection.

ACKNOWLEDGMENTS

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USPT	immuno-polymerase.clm.	1	L9
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USPT	l5 and pcr.clm.	1	L7
USPT	cd4.clm. and cd8.clm. and (bead or microbead or surface or solid or support).clm. and pcr.clm.	0	L6
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4/6,KWIC/15 (Item 1 from file: 73)

07544887 EMBASE No: 1999022804
Course and diagnostic significance of nodular gastritis in children with Helicobacter pylori **infection**
EVOLUTION ET VALEUR DIAGNOSTIQUE DE LA GASTRITE NODULAIRE AU COURS DE L'INFECTION A **HELICOBACTER PYLORI** CHEZ L'ENFANT
1998

Course and diagnostic significance of nodular gastritis in children with Helicobacter pylori **infection**
EVOLUTION ET VALEUR DIAGNOSTIQUE DE LA GASTRITE NODULAIRE AU COURS DE L'INFECTION A **HELICOBACTER PYLORI** CHEZ L'ENFANT
Kalach N.; **Raymond J.** ; Benhamou P.H.; Barhoum M.; Barjonet G.; Barbet P.; Bergeret M.; Senouci L.; Dupont...

...was to evaluate the clinical and histological features of nodular gastritis (NG), its relationships with **Helicobacter pylori** infection, and its course after H. **pylori** eradication. Patients and methods: 270 children who underwent outpatient upper gastrointestinal endoscopy at the Saint...

...institutions. Antral biopsy specimens were obtained during endoscopy. Patients with a positive biopsy for H. **pylori** by culture and/or histology were classified as H. **pylori** -positive. A clinical evaluation and a repeat endoscopy with biopsy collection were done one month...

...gastritis with a follicular architecture. Among the 43 noninstitutionalized patients with NG, 37 were H. **pylori** -positive and six were H. **pylori** -negative ($P<0.05$). All 12 institutionalized patients with NG were H. **pylori** -positive. Of the H. **pylori** -positive NG patients, 25 noninstitutionalized and six institutionalized subjects received amoxicillin, metronidazole, and lansoprazole. At reevaluation, 20 noninstitutionalized patients were H. **pylori** -negative; four of these 20 and three of the five H. **pylori** -positive patients had persistent NG. Among the six institutionalized patients who were given therapy, three converted to H. **pylori** -negative, and one of these three had persistent NG. Conclusion. H. **pylori** infection is common in children with NG. However, this association seems to be nonspecific, since some cases of NG resolve prior to H. **pylori** eradication, whereas others persist despite H. **pylori** eradication.
MEDICAL DESCRIPTORS:
disease course; **helicobacter pylori** ; histopathology; gastrointestinal endoscopy; stomach biopsy; clinical feature; treatment outcome; human; major clinical study; human tissue...

4/6,KWIC/16 (Item 2 from file: 73)

07533704 EMBASE No: 1999016474
The urea-sup 1sup 3C breath test in the course of Helicobacter pylori **gastric infection in children**
LE TEST RESPIRATOIRE A L'UREE-sup 1sup 3C AU COURS DE L'INFECTION GASTRIQUE A **HELICOBACTER PYLORI** CHEZ L'ENFANT
1998

The urea-sup 1sup 3C breath test in the course of Helicobacter pylori **gastric infection in children**
...TEST RESPIRATOIRE A L'UREE-sup 1sup 3C AU COURS DE L'INFECTION GASTRIQUE A **HELICOBACTER PYLORI** CHEZ L'ENFANT
Kalach N.; Benhamou P.H.; Briet F.; **Raymond J.** ; Dupont C.

Helicobacter pylori gastric infection in children is a public health problem. Classical diagnostic tools such as endoscopy...

...appropriate alternative method. The principle of the test relies upon the indirect detection of H **pylori** through its high urease activity. The test uses a stable (ie, non radioactive) isotope, which...

...its repeated use. The main indications are the detection and the follow-up of H **pylori** infection.
MEDICAL DESCRIPTORS:
*breath analysis; ***helicobacter pylori** ; *stomach disease--diagnosis--di ; *gram negative infection--diagnosis--di

4/6,KWIC/17 (Item 3 from file: 73)

07356218 EMBASE No: 1998227328
Spiramycin as an alternative to amoxicillin treatment associated with lansoprazole/metronidazole for Helicobacter pylori **infection in children [3]**
1998

Spiramycin as an alternative to amoxicillin treatment associated with lansoprazole/metronidazole for Helicobacter pylori **infection in children [3]**
Kalach N.; **Raymond J.** ; Benhamou P.H.; Bergeret M.; Senouci L.; Gendrel D.; Dupont C.
MEDICAL DESCRIPTORS:
helicobacter pylori ; disease association; treatment indication; antimicrobial activity; allergy--side effect--si; human; child; letter; priority journal

4/6,KWIC/18 (Item 4 from file: 73)

07253086 EMBASE No: 1998085834
The sup 1sup 3carbon urea breath test for the noninvasive detection of Helicobacter pylori **in children: Comparison with culture and determination of minimum analysis requirements**
1998

The sup 1sup 3carbon urea breath test for the noninvasive detection of Helicobacter pylori **in children: Comparison with culture and determination of minimum analysis requirements**
Kalach N.; Briet F.; **Raymond J.** ; Benhamou P.-H.; Barbet P.; Bergeret M. ; Senouci L.; Maurel M.; Flourie B.; Dupont...

...the accuracy of the labelled sup 1sup 3carbon urea breath test for the diagnosis of **Helicobacter pylori** in children and to simplify the sup 1sup 3carbon urea breath test in identifying the most discriminating sampling time. Methods: H. **pylori** was searched for in 100 children aged 10.5 +/- 4.5 years by histology, bacteriological...
MEDICAL DESCRIPTORS:
bacterium detection; **helicobacter pylori** ; breath analysis; diagnostic accuracy; diagnostic value; human; male; female; major clinical study; adolescent; child; adult...

4/6,KWIC/19 (Item 5 from file: 73)

07188167 EMBASE No: 1998080495
Evaluation of tritherapy with amoxicillin, metronidazole, and lansoprazole in the treatment of Helicobacter pylori **infection in institutionalized mentally-disabled children**
EVALUATION D'UNE TRIPLE THERAPIE AMOXICILLINE-METRONIDAZOLE- LANSOPRAZOLE DANS LE TRAITEMENT DE L'INFECTION A **HELICOBACTER PYLORI** (H. **PYLORI**) CHEZ LES ENFANTS HANDICAPES MENTAUX INSTITUTIONNALISES DANS UN CENTRE DE

LONG SEJOUR
1998

Evaluation of tritherapy with amoxicillin, metronidazole, and lansoprazole in the treatment of Helicobacter pylori **infection in institutionalized mentally-disabled children**
EVALUATION D'UNE TRIPLE THERAPIE AMOXICILLINE-METRONIDAZOLE- LANSOPRAZOLE DANS LE TRAITEMENT DE L'INFECTION A **HELICOBACTER PYLORI** (H. **PYLORI**) CHEZ LES ENFANTS HANDICAPES MENTAUX INSTITUTIONNALISES DANS UN CENTRE DE LONG SEJOUR
Kalach N.; **Raymond J.** ; Benhamou P.H.; Barbet P.; Briet F.; Bergeret M.; Hall D.; Senouci L.; Boutin...

...metronidazole combination given with an inhibitor of gastric acid secretion (lansoprazole) in the treatment of **Helicobacter pylori** infection in mentally-disabled children. Patients and methods: H. **pylori** infection was diagnosed based on cultures and histologic studies of gastirc specimens obtained from 22...

...Conclusion: Tritherapy with amoxicillin, metronidazole, and lasopraxole is associated with a low rate of H. **pylori** eradication after one and six months in mentally-disabled children.
MEDICAL DESCRIPTORS:
*__helicobacter pylori__ ; *gram negative infection--diagnosis--di; *gram negative infection--drug therapy--dt

4/6,KWIC/20 (Item 6 from file: 73)

06443459 EMBASE No: 1996108002
Randomly amplified polymorphic DNA analysis in suspected laboratory Helicobacter pylori **infection (19)**
1996

Randomly amplified polymorphic DNA analysis in suspected laboratory Helicobacter pylori **infection (19)**
Raymond J. ; Bingen E.; Brahimi N.; Bergeret M.; Kalach N.
MEDICAL DESCRIPTORS:
*__helicobacter pylori__ ; *random amplified polymorphic dna

4/6,KWIC/21 (Item 7 from file: 73)

06243630 EMBASE No: 1995280770
Isolation of Helicobacter pylori **in a six-day-old newborn (1)**
1995

Isolation of Helicobacter pylori **in a six-day-old newborn (1)**
Raymond J. ; Bargaoui K.; Kalach N.; Bergeret M.; Barbet P.; Dupont C.
MEDICAL DESCRIPTORS:
*__helicobacter pylori__ ; *gram negative infection--diagnosis--di; *gram negative infection--drug therapy--dt; *newborn infection

4/6,KWIC/22 (Item 8 from file: 73)

06196753 EMBASE No: 1995199215
Campylobacter pylori **gastric infections in the infant**
LES INFECTIONS GASTRIQUES A **HELICOBACTER PYLORI** CHEZ L'ENFANT
1995

Campylobacter pylori **gastric infections in the infant**
LES INFECTIONS GASTRIQUES A **HELICOBACTER PYLORI** CHEZ L'ENFANT
Kalach N.; Benhamou P.-H.; **Raymond J.** ; Briet F.; Fluorie B.; Senouci L.

; Dupont C.
MEDICAL DESCRIPTORS:
*helicobacter pylori ; *gastritis--drug therapy--dt

4/6,KWIC/23 (Item 1 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

11857461 BIOSIS NO.: 199900103570
The urea-13C breath test in the course of Helicobacter pylori **gastric infection in children.**
1998

The urea-13C breath test in the course of Helicobacter pylori **gastric infection in children.**
...AUTHOR: **Raymond J**

ABSTRACT: **Helicobacter pylori** gastric infection in children is a public health problem. Classical diagnostic tools such as endoscopy...

...appropriate alternative method. The principle of the test relies upon the indirect detection of H. **pylori** through its high urease activity. The test uses a stable (i.e, non radioactive) isotope...

...its repeated use, The main indications are the detection and the follow-up of H. **pylori** infection.
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives
DISEASES: **Helicobacter pylori** gastric infection...

4/6,KWIC/24 (Item 2 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

11783615 BIOSIS NO.: 199900029724
Molecular evidence for intrafamilial tranmission of Helicobacter pylori
.
1998

Molecular evidence for intrafamilial tranmission of Helicobacter pylori
.
AUTHOR: **Raymond J** ...
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives
DISEASES: **Helicobacter -pylori** infection...
ALTERNATE INDEXING: **Helicobacter** Infections (MeSH)

4/6,KWIC/25 (Item 3 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

11743544 BIOSIS NO.: 199800524240
Inflammation and chronic infections in unstable coronary artery disease.
1998

...AUTHOR: **Raymond A**
DESCRIPTORS:
...ORGANISMS: **Helicobacter -pylori** (Aerobic Helical or Vibrioid Gram-Negatives
...DISEASES: **Helicobacter** infection

4/6,KWIC/26 (Item 4 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

11683630 BIOSIS NO.: 199800465361
Value of the association amoxicillin, clarithromycin and lansoprazole in short-term treatment of gastric infection due to Helicobacter pylori **(H.** pylori**) in children.**
1998

...**the association amoxicillin, clarithromycin and lansoprazole in short-term treatment of gastric infection due to** Helicobacter pylori **(H.** pylori**) in children.**
...AUTHOR: **Raymond J**
DESCRIPTORS:
...ORGANISMS: **Helicobacter -pylori** (Aerobic Helical or Vibrioid Gram-Negatives
DISEASES: **Helicobacter -pylori** infection...

4/6,KWIC/27 (Item 5 from file: 5)

11683629 BIOSIS NO.: 199800465360
Helicobacter pylori **(H.** pylori**) infection and statural growth.**
1998

Helicobacter pylori **(H.** pylori**) infection and statural growth.**
...AUTHOR: **Raymond J**
DESCRIPTORS:
...ORGANISMS: **Helicobacter -pylori** (Aerobic Helical or Vibrioid Gram-Negatives
DISEASES: **Helicobacter -pylori** infection...

4/6,KWIC/28 (Item 6 from file: 5)

11683628 BIOSIS NO.: 199800465359
Influence of intrafamilial spread of Helicobacter pylori **(H.** pylori**) gastric infection on eradication rate in children.**
1998

Influence of intrafamilial spread of Helicobacter pylori **(H.** pylori**) gastric infection on eradication rate in children.**
...AUTHOR: **Raymond J**
DESCRIPTORS:
...ORGANISMS: **Helicobacter -pylori** (Aerobic Helical or Vibrioid Gram-Negatives
DISEASES: **Helicobacter -pylori** infection...

4/6,KWIC/29 (Item 7 from file: 5)

11606529 BIOSIS NO.: 199800388265
Spiramycin as an alternative to amoxicillin treatment associated with lansoprazole/metronidazole for Helicobacter pylori **infection in children.**
1998

Spiramycin as an alternative to amoxicillin treatment associated with lansoprazole/metronidazole for Helicobacter pylori **infection in children.**
...AUTHOR: **Raymond J**
DESCRIPTORS:
...ORGANISMS: **Helicobacter -pylori** (Aerobic Helical or Vibrioid Gram-Negatives
DISEASES: **Helicobacter pylori** infection...

4/6,KWIC/30 (Item 8 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

10874584 BIOSIS NO.: 199799495729
Influence of antimicrobial resistance on eradication of Helicobacter pylori **in infected children.**
1996

Influence of antimicrobial resistance on eradication of Helicobacter pylori **in infected children.**
AUTHOR: **Raymond J** ...
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives)

4/6,KWIC/31 (Item 9 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

10873399 BIOSIS NO.: 199799494544
Molecular analysis provides rapid differentiation of Helicobacter pylori **clinical isolates.**
1996

Molecular analysis provides rapid differentiation of Helicobacter pylori **clinical isolates.**
AUTHOR: **Raymond J** ...
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives)
MISCELLANEOUS TERMS: ...**HELICOBACTER PYLORI** INFECTION

4/6,KWIC/32 (Item 10 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

10543164 BIOSIS NO.: 199699164309
Controlled study of the efficacy of lansoprazole associated with two dual antibiotic therapies in treating gastric Helicobacter pylori **infection in children.**
1996

...**study of the efficacy of lansoprazole associated with two dual antibiotic therapies in treating gastric** Helicobacter pylori **infection in children.**
AUTHOR: **Raymond J** ...
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives

4/6,KWIC/33 (Item 11 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

10543001 BIOSIS NO.: 199699164146
Kinetic analysis and simplification of respiratory test with 13C-urea for diagnosing Helicobacter pylori **(H. pylori) infection in children.**
1996

Kinetic analysis and simplification of respiratory test with 13C-urea for diagnosing Helicobacter pylori **(H. pylori) infection in children.**
...AUTHOR: **Raymond J**
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives

4/6,KWIC/34 (Item 12 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

10542931 BIOSIS NO.: 199699164076
Evolution and pathognomonic value of micronodular gastritis during Helicobacter pylori **infection in children.**
1996

Evolution and pathognomonic value of micronodular gastritis during Helicobacter pylori **infection in children.**
...AUTHOR: **Raymond J**
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives

4/6,KWIC/35 (Item 13 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

10398667 BIOSIS NO.: 199699019812
Time course analysis and simplification of the 13C-urea breath test (13C-UBT) in the detection of Helicobacter pylori **infection (H.** pylori**) in children.**
1996

...**analysis and simplification of the 13C-urea breath test (13C-UBT) in the detection of** Helicobacter pylori **infection (H.** pylori**) in children.**
...AUTHOR: **Raymond J**
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives

4/6,KWIC/36 (Item 14 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

10084851 BIOSIS NO.: 199598539769
Carbon urea breath test for the detection of Helicobacter pylori **(H.** pylori**) gastric infection in children.**
1995

Carbon urea breath test for the detection of Helicobacter pylori **(H.** pylori**) gastric infection in children.**
AUTHOR: **Raymond J** ...

4/6,KWIC/37 (Item 15 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

09980191 BIOSIS NO.: 199598435109
Controlled study of the efficacy of lansoprazole associated with two different antibiotic combinations in treating gastric Helicobacter pylori **infections in children.**
1995

...**study of the efficacy of lansoprazole associated with two different antibiotic combinations in treating gastric** Helicobacter pylori **infections in children.**
...AUTHOR: **Raymond J**
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives

4/6,KWIC/38 (Item 16 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

09980190 BIOSIS NO.: 199598435108
Serological studies of gastric Helicobacter pylori **infections in children.**
1995

Serological studies of gastric Helicobacter pylori **infections in children.**
...AUTHOR: **Raymond J**
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives

4/6,KWIC/39 (Item 17 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

09923245 BIOSIS NO.: 199598378163
Helicobacter pylori **infections in children: Many questions, a few answers.**
1995

Helicobacter pylori **infections in children: Many questions, a few answers.**
...AUTHOR: **Raymond J**
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives)

4/6,KWIC/40 (Item 18 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

09804843 BIOSIS NO.: 199598259761
A controlled study of the efficacy of lansoprazole in combination with two differents dual antibiotic associations during Helicobacter pylori **(H.** pylori**) gastric infection in children.**
1995

...**study of the efficacy of lansoprazole in combination with two differents dual antibiotic associations during** Helicobacter pylori **(H.** pylori**) gastric infection in children.**
...AUTHOR: **Raymond J**
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives

4/6,KWIC/41 (Item 19 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

09571272 BIOSIS NO.: 199598026190
Prevalence of Helicobacter pylori **Infection in Encephalopathic Children Living in Institution.**
1994

Prevalence of Helicobacter pylori **Infection in Encephalopathic Children Living in Institution.**
AUTHOR: **Raymond J** ...
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives

4/6,KWIC/42 (Item 20 from file: 5)
DIALOG(R)File 5:(c) 2001 BIOSIS. All rts. reserv.

09432396 BIOSIS NO.: 199497440766

Evaluation of two years of research of Helicobacter pylori **in children.**
1993

Evaluation of two years of research of Helicobacter pylori **in children.**
AUTHOR: **Raymond J** ...
DESCRIPTORS:
...ORGANISMS: **Helicobacter pylori** (Aerobic Helical or Vibrioid Gram-Negatives)

4/6,KWIC/43 (Item 1 from file: 144)
DIALOG(R)File 144:(c) 2001 INIST/CNRS. All rts. reserv.

13858392 PASCAL No.: 99-0035919
Le test respiratoire a l'uree- SUP 1 SUP 3 C au cours de l'infection gastrique a Helicobacter pylori **chez l'enfant**
(The urea- SUP 1 SUP 3 C breath test in the course of Helicobacter pylori **gastric infection in children)**
1998

...**a l'uree- SUP 1 SUP 3 C au cours de l'infection gastrique a** Helicobacter pylori **chez l'enfant**
(The urea- SUP 1 SUP 3 C breath test in the course of Helicobacter pylori **gastric infection in children)**
KALACH N; BENHAMOU P H; BRIET F; **RAYMOND J** ; DUPONT C
L'infection gastrique a **Helicobacter pylori** chez l'enfant represente un important enjeu de sante publique. Les methodes diagnostiques classiques font...

... alternative, Le principe de ce test repose sur la mise en evidence indirecte de H **pylori** grace a son activite ureasique. Il s'agit d'un test non radioactif permettant son...
... trouve ses indications principales dans le depistage et le suivi de l'infection a H **pylori** .

English Descriptors: **Helicobacter pylori** ; Stomach; Gastritis; Diagnosis ; Breath test; Child; Urea; Mass spectrometry; Isotopes; Carbon; Bacteriosis

French Descriptors: **Helicobacter pylori** ; Estomac; Gastrite; Diagnostic; Test respiratoire; Enfant; Uree; Spectrometrie masse; Isotope; Carbone; Bacteriose

Spanish Descriptors: **Helicobacter pylori** ; Estomago; Gastritis; Diagnostico; Test respiratorio; Nino; Urea; Espectrometria masa; Isotopo; Carbono; Bacteriosis

4/6,KWIC/44 (Item 2 from file: 144)
DIALOG(R)File 144:(c) 2001 INIST/CNRS. All rts. reserv.

13578279 PASCAL No.: 98-0280894
Prevalence de l'infection a Helicobacter pylori **chez l'enfant en fonction de l'age : etude retrospective**
(Prevalence of helicobacter pylori **infection in children depending on their age. A retrospective study)**
1998

Prevalence de l'infection a Helicobacter pylori **chez l'enfant en fonction de l'age : etude retrospective**
(Prevalence of helicobacter pylori **infection in children depending on their age. A retrospective study)**
RAYMOND J ; KALACH N; BERGERET M; SAUVE-MARTIN H; BENHAMOU P; DUPONT C

L'objectif de l'etude etait d'evaluer la prevalence de l'infection a H **pylori** dans une population d'enfants parisienne. Patients et methodes. - Pendant une periode de 3 ans, l'infection a H **pylori** a ete recherchee chez 623 enfants consultant dans notre hopital. Il s'agissait soit d...

... abdominales recidivantes depuis plus de 3 mois pour lesquels le diagnostic d'infection a H **pylori** etait evoque, soit d'un groupe d'enfants temoin qui presentaient des troubles a type...

... preuve de l'infection etait recherchee par serologie. Le dosage serique des anticorps anti-H **pylori** a ete realise selon la technique Elisa, Cobas Core Roche, IgG, 2 SUP e generation, Roche, France. Resultats. - L'infection a H **pylori** a ete prouvee chez 99 enfants sur 623 (15,8 %). n n'y avait pas...

...l'age, le sexe, l'origine ethnique et la prevalence de l'infection a H **pylori** . Le taux d'acquisition de l'infection est de 2,1 % par annee d'age ...

... chez l'adulte, ce qui est vraisemblablement en faveur d'une acquisition precoce d'H **pylori** dans la vie.

English Descriptors: **Helicobacter pylori** ; Bacteriosis; Age; Immunological investigation; Serology; Child; Prevalence; Retrospective

French Descriptors: **Helicobacter pylori** ; Bacteriose; Age; Exploration immunologique; Serologie; Enfant; Prevalence; Retrospective

Spanish Descriptors: **Helicobacter pylori** ; Bacteriosis; Edad; Analisis inmunologico; Serologia; Nino; Prevalencia; Retrospectiva

4/6,KWIC/45 (Item 3 from file: 144)
DIALOG(R)File 144:(c) 2001 INIST/CNRS. All rts. reserv.

13473718 PASCAL No.: 98-0170765
The SUP 1 SUP 3 carbon urea breath test for the noninvasive detection of Helicobacter pylori **in children : Comparison with culture and determination of minimum analysis requirements**
1998

The SUP 1 SUP 3 carbon urea breath test for the noninvasive detection of Helicobacter pylori **in children : Comparison with culture and determination of minimum analysis requirements**
KALACH N; BRIET F; **RAYMOND J** ; BENHAMOU P H; BARBET P; BERGERET M; SENOUCI L; MAUREL M; FLOURIE B; DUPONT
... of the labelled SUP 1 SUP 3 carbon urea breath test for the diagnosis of **Helicobacter pylori** in children and to simplify the SUP 1 SUP 3 carbon urea breath test in identifying the most discriminating sampling time. Methods: H. **pylori** was searched for in 100 children aged 10.5 +- 4.5 years by histology, bacteriological...

English Descriptors: Campylobacter infection; **Helicobacter pylori** ; Diagnosis; Measurement; Enzymatic activity; Urease; Breath test; Non invasive method; Performance evaluation; Human

French Descriptors: Campylobacteriose; **Helicobacter pylori** ; Diagnostic; Mesure; Activite enzymatique; Urease; Test respiratoire; Methode non invasive; Evaluation performance; Homme

Spanish Descriptors: Campilobacteriosis; **Helicobacter pylori** ; Diagnostico; Medida; Actividad enzimatica; Urease; Test respiratorio; Metodo no invasivo; Evaluacion prestacion; Hombre

4/6,KWIC/46 (Item 4 from file: 144)
DIALOG(R)File 144:(c) 2001 INIST/CNRS. All rts. reserv.

13415946 PASCAL No.: 98-0109154
Evaluation d'une triple therapie amoxicilline-metronidazole-lansoprazole dans le traitement de l'infection a Helicobacter pylori **(H. pylori) chez les enfants handicapes mentaux institutionnalises dans un centre de long sejour**
(Evaluation of tritherapy with amoxicillin metronidazole, and lansoprazole in the treatment of helicobater pylori **infection in institutionalized mentally-disabled children)**
1998

Evaluation d'une triple therapie amoxicilline-metronidazole-lansoprazole dans le traitement de l'infection a Helicobacter pylori **(H. pylori) chez les enfants handicapes mentaux institutionnalises dans un centre de long sejour**
(Evaluation of tritherapy with amoxicillin metronidazole, and lansoprazole in the treatment of helicobater pylori **infection in institutionalized mentally-disabled children)**
KALACH N; **RAYMOND J** ; BENHAMOU P; BARBET P; BRIET F; BERGERET M; HALL D; SENOUCI L; BOUTIN A...

... combinaison avec un anti-secretoire gastrique (lansoprazole) dans le traitement de l'infection a H. **pylori** chez les enfants handicapes mentaux. Patients et methodes: L'infection a H. **pylori** a ete recherchee et diagnostiquee par culture et examen anatomopathologique chez 22 enfants handicapes mentaux...

... ont ete traites par la triple therapie amoxicilline-metronidazole-lansoprazole (AML). L'eradication d'H. **pylori** etait controlee par la culture et l'examen anatomopathologique un mois apres la fin du...

...ne permet d'obtenir qu'un faible taux d'eradication de l'infection a H. **pylori** chez les enfants handicapes mentaux a un et six mois.

English Descriptors: **Helicobacter pylori** ; Bacteriosis; Digestive diseases; Treatment efficiency; Specialized institution; Child; Mental retardation; Handicap; Lansoprazole; Combined treatment; Amoxicillin...

French Descriptors: **Helicobacter pylori** ; Bacteriose; Appareil digestif pathologie; Efficacite traitement; Institution specialisee; Enfant; Arrieration mentale; Handicap; Lansoprazole; Traitement associe...

Spanish Descriptors: **Helicobacter pylori** ; Bacteriosis; Aparato digestivo patologia; Eficacia tratamiento; Institucion especializada; Nino; Retraso mental; Desventaja; Lansoprazol; Tratamiento asociado...

4/6,KWIC/47 (Item 5 from file: 144)
DIALOG(R)File 144:(c) 2001 INIST/CNRS. All rts. reserv.

12063802 PASCAL No.: 95-0263731
Helicobacter pylori **chez l'enfant : beaucoup de questions, quelques reponses**
(Helicobacter pylori **in child: many questions, many responses)**
1995

Helicobacter pylori **chez l'enfant : beaucoup de questions, quelques reponses**
(Helicobacter pylori **in child: many questions, many responses)**
BENHAMOU P H; KALACH N; **RAYMOND J** ; DUPONT C

English Descriptors: Gastritis; Child; Pain; Abdomen; **Helicobacter pylori** ; Review

Pathophysiology, diagnostic and treatment of the chronic abdominal pain in children

FISIOPATOLOGIA, DIAGNOSTICO Y TRATAMIENTO DEL DOLOR ABDOMINAL CRONICO EN EL NINO

Carnicer De La Pardina J.
Av. Francesc Macia 2,08206 Sabadell Spain

DOLOR (DOLOR) (Spain) 1995, 10/4 (249-257)
CODEN: DOLOF ISSN: 0214-0659
DOCUMENT TYPE: Journal; Review
LANGUAGE: SPANISH SUMMARY LANGUAGE: ENGLISH; SPANISH

Chronic or recurrent abdominal pain is a frequent symptom in school-age children and adolescents. It may be caused by multiple disorders. Besides organic causes of chronic abdominal pain, three clinical presentations of psychosomatic or functional recurrent abdominal pain have been described in children and adolescents: periumbilical **paroxysmal** pain, non-ulcer dyspepsia, and irritable bowel syndrome. The pathophysiology, diagnostic approach, and management of chronic abdominal pain are revised. The characteristics of the pain pattern suggesting an organic cause of chronic abdominal pain are described. In the recent years, the technical advances and the increasing use of some diagnostic procedures have evidenced that organic causes of chronic abdominal pain are more frequent than previously suspected. In addition, new etiologies have been identified, like **Helicobacter pylori** associated gastritis.

WEST

Generate Collection

L4: Entry 6 of 29 File: USPT Oct 5, 1999

US-PAT-NO: 5962223
DOCUMENT-IDENTIFIER: US 5962223 A

TITLE: Detection of specific sequences in nucleic acids

DATE-ISSUED: October 5, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Whiteley; Norman M.	San Carlos	CA	N/A	N/A
Hunkapiller; Michael W.	San Carlos	CA	N/A	N/A
Glazer; Alexander N.	Orinda	CA	N/A	N/A

US-CL-CURRENT: 435/6; 435/5, 435/810, 435/91.5, 435/91.52, 536/24.3, 536/24.31, 536/24.32, 536/24.33

CLAIMS:

We claim:
1. A kit for determining the presence or absence of a target polynucleotide sequence in a nucleic acid sample, said kit comprising:
a first probe which is complementary to a first region of a target sequence,
a second probe which is complementary to a second region of the target sequence, where said first and second target regions are contiguous with one another, and said first and second probes are capable of being ligated to each other when hybridized to such contiguous first and second target regions,
a third probe which is complemnentary to a third target region of the target sequence which is continuous with the first target region, such that said second and third target regions correspond to alternative allelic sequences or to a normal and mutated sequence, and
ligation means capable of ligating first and second probes, or first and third probes, that have hybridized specifically to contiguous target regions to which the first and second probes, or first and third probes, are complementary, respectively.
2. The kit of claim 1, wherein said ligation means is a ligase enzyme.
3. The kit of claim 1, wherein at least one of said probes contains a label that allows specific detection of said labeled probe in the presence of unlabeled nucleic acids.
4. The kit of claim 3, wherein said label is radioactive.
5. The kit of claim 3, wherein said label is a fluorescent label.
6. The kit of claim 3, wherein said label is an enzyme.
7. The kit of claim 1, wherein at least one of said probes includes non-polynucleotide hook moiety for capture of the probe on a support.
8. The kit of claim 7, wherein said hook moiety is a biotin moiety.
9. The kit of claim 7, wherein said hook moiety is an antigen, and the kit further includes an antibody which is immunospecific for the antigen.
10. The kit of claim 7, wherein said hook moiety is a ligand, and the kit further includes a receptor which can bind specifically to the ligand.
11. The kit of claim 1, which further includes instructions for performing ligation of the first and second probes, or first and third probes, when bound to contiguous target regions, to detect whether a target polynucleotide sequence complementary to the first and second probes, or first and third probes, is present in the sample.
12. The kit of claim 11, wherein said ligation means is a ligase enzyme.
13. The kit of claim 11, wherein at least one of said probes contains a label that

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L11: Entry 5 of 11 File: USPT Jul 13, 1999

DOCUMENT-IDENTIFIER: US 5922553 A
TITLE: Method of detecting protein by immuno RNA

BSPR:
Recently, Sano et al., 1992 Science, 258:120-122, described an antigen detection technique termed immuno-polymerase chain reaction (immuno-PCR). This procedure provides an extremely sensitive method to detect proteins. In immuno-PCR, a linker molecule with bi-specific binding affinity for DNA and antibody is used to attach a marker DNA molecule specifically to an antigen-antibody complex, thus resulting in the formation of a specific antigen-antibody-DNA conjugate. The attached marker DNA can be amplified by PCR with the appropriate primers. The presence of specific size PCR products demonstrates that marker DNA molecules are attached specifically to antigen-antibody complexes thereby indicating the presence of antigen. As described by Sano et al. 1992, antigen is immobilized on the surface of microtiter plates and then detected by immuno-PCR. Using this technique, an approximately 10.sup.5 increase in sensitivity over an alkaline phosphatase conjugated ELISA was obtained. Sensitivity advantages of immuno-PCR have subsequently been confirmed in assays for mouse anti-lipoprotein IgG (Ruzicka et al., 1993 Science, 260:698-699); a human proto-oncogene protein (Zhou et al., 1993 Nucleic Acid Res., 21:6038-6039); and tumor necrosis factor alpha (Sanna et al., 1995 Proc. Natl. Acad. Sci., 92:272-275).

ORPL:
Suzuki et al., "Double Determinant Immuno-Polymerase Chain Reaction: A SSensitive Method for Detecting Circulating Antigens in Human Sera", 1995 Jpn. J. Cancer Res., 86:885-889.

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Suzuki et al., "Double Determinant Immuno-Polymerase Chain Reaction: A Sensitive Method for Detecting Circulating Antigens in Human Sera", 1995 Jpn. J. Cancer Res., 86:885-889.

Double **determinant immuno-polymerase** chain **reaction for detecting soluble intercellular adhesion molecule-1.**

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A sensitive method for the detection of antigens in sera, termed double determinant immuno-polymerase chain reaction (DDI-PCR), was developed using two monoclonal antibodies (MoAbs) in which the antigens are sandwiched and a specific DNA molecule as a marker. Instead of the antigen itself, the first MoAb to bind the circulating antigens was immobilized. After the biotinylated second MoAb was bound to the antigen, free streptavidin was used to attach a biotinylated DNA to the biotinylated second MoAb. The biotinylated DNA complexed with antigen-antibody-streptavidin was amplified by PCR. The PCR products were analyzed by Southern blot hybridization after agarose gel electrophoresis. Compared with the conventional ELISA using soluble intercellular adhesion molecule-1 (sICAM-1) in the supernatant of cultured Panc-1 cells as an antigen, our DDI-PCR was 10(3) times more sensitive in detection limit. In both the culture medium and sera from gastric cancer patients of high sICAM-1 titer, an approximately 10(3)-fold enhancement in detection sensitivity was obtained compared with ELISA. In addition, the DDI-PCR system can detect the antigen in sera at a level below the detection limit of traditional ELISA methods with high sensitivity. Thus, DDI-PCR has the significant advantage that it can be readily applied to any antigen-antibody system with two MoAbs without making any original molecules.

Tags: Animal; Comparative Study; Support, Non-U.S. Gov't
Descriptors: *Intercellular Adhesion Molecule-1--Metabolism--ME; Antibodies, Monoclonal--Immunology--IM; Antibodies, Monoclonal-

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L32: Entry 1 of 2 File: USPT Jul 13, 1999

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TITLE: Method of detecting protein by immuno RNA

DATE-ISSUED: July 13, 1999

INVENTOR-INFORMATION:

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US-CL-CURRENT: 435/7.92; 435/6, 435/7.94, 436/518

CLAIMS:

What is claimed is:
1. A method for quantifying levels of a selected protein by immuno-aRNA comprising:
a) immobilizing a first antibody targeted to a selected protein to a solid support;
b) contacting the solid support with the selected protein so that the selected protein binds to the immobilized first antibody;
c) contacting the solid support with a RNA promoter-driven cDNA sequence covalently coupled to a second antibody targeted to the selected protein so that the second antibody binds to the bound selected protein on the solid support; and
d) quantifying levels of the promoter-driven cDNA sequence covalently coupled to the bound second antibody by amplified RNA techniques as an indication of the amount of selected protein present.
2. The method of claim 1 wherein a T7 promoter driven cDNA sequence is covalently coupled to the second antibody.
3. The method of claim 1 wherein the selected protein is tau.